Conferences and Reviews

Hansen's Disease

Discussant
ROBERT H. GELBER, MD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

HOMER BOUSHEY, MD*: *The topic of this conference—Hansen's disease—will be discussed by Robert Gelber, MD. Dr Gelber has been active in the study of the interplay between the infecting organism, the immune responsiveness of the host, and the action of pharmacologic agents in modifying Hansen's disease. On the basis of knowledge obtained from his work, he is able to project how modern advances in pharmacology, in antibiotics, and perhaps in the development of vaccines will change the expression of this important disease in the next decade.*

Hansen's Disease and Social Stigma

ROBERT H. GELBER, MD†: In 1873, a Norwegian physician, Gerhard Henrik Armauer Hansen, discovered that a bacterium, *Mycobacterium leprae,* was the cause of an age-old disease, leprosy. To that time, a relationship between a specific bacterium and a human disease had been established only for anthrax. Today we call leprosy "Hansen's disease," not so much to honor Hansen's discovery but because the words "leprosy" and "leper" have such negative connotations; it is hoped that this more neutral name may help in the difficult task of reducing the social stigma from which patients still suffer enormously. The horror of leprosy largely results from the fact that *M leprae* is the only bacterium that invades peripheral nerves, resulting in neuropathy that in turn results in myopathy and insensitivity—particularly to pain, temperature, and fine touch. This insensitivity allows for trauma, secondary infection, deformity, and at times amputation of the distal extremities. In the Bible "lepers" were judged "unclean" and placed "outside the camp." Yet, it is noteworthy that biblical "leprosy" was not leprosy itself but probably certain other disfiguring dermatologic diseases. Leprosy originated in China or India and did not arrive in the Middle East until long after the biblical era. Nevertheless, in western society, this diagnosis continues to carry a social stigma. Also, in Asian societies, patients with leprosy are often ostracized; in traditional Chinese families, those discovered to have the disease are often told to "never darken the door again."

With early diagnosis and modern therapy, the severe neurologic sequelae of leprosy can fortunately now be largely prevented, and patients are now more likely to suffer from the psychosocial aspects of their disease than from the actual medical effects. In the lay press, patients with the acquired immunodeficiency syndrome (AIDS) have been referred to as "the new lepers" and as irrationally ostracized as have been Hansen's disease sufferers for centuries.

To emphasize the importance of the leprosy stigma to affected persons, I shall share an anecdote. One morning I came in to the hospital to see patients on rounds. The previous evening, the house staff had evaluated a young man from the Philippines with the initial diagnosis of lepromatous leprosy. As I came in the door I was greeted by, "Oh, Dr Gelber, I guess you are the one who knows about this. Am I really one of the living dead?" I was startled by this question, not knowing where the idea came from, and eventually found out that in Europe in the Middle Ages, when people were diagnosed with the illness, they were declared by the church as legally dead and all their material goods were distributed. Because much of the culture of the Philippines emanated from Spain, that idea has stuck. Furthermore, before the introduction of antibiotics in the Philippines, the control of leprosy involved the removal of patients from their homes to institutions (leprosaria) and even the removal of babies at birth from affected parents. Even in these more enlightened times, when patients with leprosy are no longer put in institutions, many patients in the Philippines will hide their illness, getting progressively more deformed, rather than face the psychosocial consequences of their diagnosis and the social ostracism that attends it.

*Professor and Vice-Chair, Department of Medicine, University of California, San Francisco (UCSF), School of Medicine.

†Clinical Professor of Epidemiology and Dermatology, UCSF, and Director, Northern California Ambulatory Hansen's Disease Program, San Francisco, California.

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Reprint requests to Robert H. Gelber, MD, Director, Northern California Ambulatory Hansen's Disease Program, 2211 Post St, Suite 301, San Francisco, CA 94115.

ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli
AIDS = acquired immunodeficiency syndrome
WHO = World Health Organization

Epidemiology

Leprosy is far from a disease of the past. It is estimated by the World Health Organization (WHO) that there are more cases worldwide today than ever before in history—perhaps as many as 5.5 million.[1] The disease prevalence is highest in Africa, although most of the world's cases are found in Asia. In India, which has the most disease, it is estimated that almost 1% of the population—about 3 million people—have leprosy. The disease is also endemic in many other developing countries, particularly in Latin America, especially in the Amazon Basin of Brazil, and the Pacific.*

Although it is estimated that there are only about 6,000 cases of leprosy in the United States, the disease is on the rise in this country owing to the fact that current migration to the United States is largely from the endemic developing countries, including Latin America and Asia. In 1960 only 60 cases were reported to the Centers for Disease Control and Prevention annually; this has risen to about 150 cases to 200 cases annually. A few endemic cases occur in the United States, but these are confined to the states of Hawaii, Louisiana, and Texas. In the United States, leprosy is largely found on the West Coast (particularly California), Hawaii, and Texas. This geographic distribution reflects the preferred areas of settlement for immigrants from the Philippines, Mexico, and Southeast Asia. I treat about 650 leprosy patients here in northern California, at one of the four West Coast US Public Health Service-sponsored clinics. The other three clinics are in Los Angeles, San Diego, and Seattle. These four clinics see about 60% of the leprosy patients under treatment in the United States.

As with the major American systemic fungal diseases in their disseminated forms, lepromatous leprosy shows a considerable male-to-female predominance, being about twice as prevalent in men. Coccidioidomycosis in its disseminated form is about three times more common, disseminated histoplasmosis about four to five times more common, and systemic blastomycosis as much as six to seven times more common in men than in women.

These systemic fungal diseases share with *M leprae* infection intracellular parasitism, the protective arm of immunity for which is cell-mediated immunity. It is a well-recognized but poorly understood phenomenon that, whether it be in humans or in mice, females have enhanced immune function. This of course predisposes women to a greater prevalence of immune-mediated diseases, like lupus erythematosus and rheumatoid arthritis, but may also be protective in the case of diseases such as lepromatous leprosy. Indeed, immunologists who work with cellular immune function in mice generally choose female mice because they have more regular and profound cellular immune responses.

If there is a simple point worth emphasizing, it is that people with skin rashes and evidence of peripheral neuropathy who originate from leprosy endemic countries may indeed have leprosy. I point this out because the preceding director of Hansen's Disease Research Laboratories, Paul Fasal, MD, who retired in 1979, used to say that the mean time from medical presentation to diagnosis in California was two years. At that time Hansen's disease in California was certainly more of a rarity than it is today. Although such a delay in diagnosis is seldom seen today, it is still not unusual for patients to see several physicians and be given dermatologic preparations and at times antibiotics for a considerable period before the diagnosis is made. Thus I urge that for patients who present with peculiar rashes or signs of peripheral nerve dysfunction and who hail from endemic countries, Hansen's disease be included in the differential diagnosis.

Incubation Period

The incubation period for leprosy is uniquely long among the bacterial diseases, with a minimum of 2 to 3 years, probably an average of 5 to 7 years, and a maximum of 40 to 50 years. I know of several Filipino men in the sixth or seventh decade of life who permanently left the Philippines just after World War II and who are just now having signs and symptoms of the disease. The long incubation period is a function of two factors:

- *Mycobacterium leprae* is a slowly growing organism. As is well known, *Escherichia coli* divides in culture every 20 minutes and *Mycobacterium tuberculosis* about once a day. *M leprae* does not grow in artificial media nor—at least convincingly—in tissue culture, but in the feet of mice it divides every two weeks[2]—a very slow rate of growth indeed.
- The other factor contributing to the long incubation period of leprosy is that, among the human bacterial diseases, lepromatous leprosy accumulates by many orders of magnitude the greatest number of bacteria before a patient has signs and symptoms of disease. In these patients, though *M leprae* invades every organ system except the lungs and central nervous system, it is found preferentially in the skin, dermal nerves, and larger peripheral nerve trunks.

The skin of patients with lepromatous leprosy may contain as many as 10^9 bacilli per gram, which may result in bacilli accounting for 15% of the skin's dry weight. In untreated patients with lepromatous leprosy, there is a constant afebrile bacteremia of 10^5 bacilli per milliliter of blood.[3] To put this number in some perspective, in gram-negative sepsis or streptococcal endocarditis, it would be rare to have more than 10^3 bacteria per milliliter of blood.

Transmission

It is surprising that there is still uncertainty about how leprosy is transmitted. The commonest view was that it

*See also the editorial by R. A. Miller, MD, "Hansen's Disease—A Time for Cautious Optimism," on pages 631-633 of this issue.

was spread by skin-to-skin contact. Yet, if the skin of patients heavily infected with lepromatous leprosy is examined histologically, there are no organisms in the epidermis or the most superficial levels of the dermis. There may be situations where, because of either anesthesia and consequent trauma or lepra reactions with ulceration, the epidermis gets denuded, allowing a direct egress of the organisms from the skin. Skin-to-skin contact, however, is not currently considered a common route of disease transmission.

The most widely held view of transmission is that it occurs by nasal droplet infection, and the evidence for this is somewhat convincing. Immunosuppressed rodents placed in an aerosol of *M leprae* become diseased,[4] and the number of organisms in a sneeze from a patient with untreated lepromatous leprosy is about the same as that in a cough from a patient with untreated cavitary pulmonary tuberculosis.[5]

Other possible means of transmission may also be important, and the one that is most attractive, although it is essentially unproved, is that of direct dermal inoculation. Such an alternative hypothesis seems necessary to explain the epidemiology of leprosy in India. Tuberculosis in India, as might be expected of a pathogen spread by the respiratory route, is an urban disease. On the other hand, leprosy in India is largely a rural disease[6] and is especially prevalent in persons whose occupations bring them in close contact with the soil. Furthermore, *M leprae* can be found in the soil,[7,8] people in endemic countries often do not wear shoes, and direct dermal inoculation may result in leprosy transmission. There was an infamous tattoo parlor in Hong Kong where a few sailors who were tattooed came down with the disease[9]; clearly the tattoo needles were not being properly sterilized. Also, one of my colleagues, when attempting to inoculate a mouse footpad with *M leprae,* missed the mouse, hitting his finger. A couple of months later there was a nodule at the site of the needle stick that when a biopsy was taken showed granulomas and acid-fast bacilli. Thus, there are reasons to think that direct dermal inoculation may also be a route of leprosy transmission.

In terms of alternative routes of disease transmission, bed bugs and mosquitos in the vicinity of leprosaria regularly harbor *M leprae,*[10] and mosquitos, after biting patients with lepromatous leprosy, are able to transmit *M leprae* to mice as long as 48 hours later.[11] When I worked at the National Institute for Medical Research in London, we conducted an experiment with *Mycobacterium lepraemurium,* which causes a mouse mycobacterial disease that results in a high level of bacteremia (10^7 bacilli per milliliter of blood). In this study, we infected mice with *M lepraemurium* and had mosquitos bite these mice. Later, the mosquitos were allowed to feed on uninfected mice; by these means, we were able to transmit this mycobacterial disease for as long as five days after the original blood meal.

It is still uncertain how the organism is spread, and there are grounds for there being several routes of disease propagation. It could be that the spectrum of the disease is not entirely a function of precedent cellular immune responses but has more to do with the inoculum size and route of infection. One of the reasons I have remained intrigued by the pathobiology of leprosy is that, despite the fact that this disease is of such historical interest, there are still such basic questions concerning its pathogenesis yet to be elucidated.

Whatever the mode of *M leprae* transmission, it is a disease that tends to reside within households. If a person in an endemic country contracts lepromatous leprosy, the chance that another person in the household will get it is about 10%. In nonendemic countries, including the United States and Holland, for reasons that remain obscure, the disease develops in household contacts of lepromatous leprosy only 1% of the time. Patients with tuberculoid leprosy, on the other hand, do not appear to be a source of disease transmission, even to persons in their immediate household.

Clinical Presentation and Disease Spectrum

Patients present with three principal manifestations: various skin rashes, consequences of the peripheral neuropathy, and chronic nasal congestion (only in the lepromatous form). The peripheral neuropathy may result in muscle weakness. The ulnar nerve is the nerve trunk most commonly involved, and this may lead to clawing of the fourth and fifth fingers and weakness and wasting of the dorsal interosseous musculature of the affected hand. If the peroneal nerve is involved, footdrop results. Hypoesthesia may result in chronic recurrent plantar ulceration, as well as burns and other trauma to the distal extremities that, when associated with secondary infection, may result in the loss of digits.

Leprosy is a disease with a distinct clinical pathologic spectrum (Table 1) associated with a range of host immunologic reactivity. At one polar extreme of the spectrum is tuberculoid leprosy, which is manifested by one or more hypopigmented anesthetic macules with distinct, often erythematous, borders (Figure 1). In tuberculoid disease, pathologic and enlarged nerve trunks often occur spatially related to the skin lesions, are generally asymmetric, and may at times be the sole physical finding ("neural leprosy"). Patients with tuberculoid leprosy histologically have dermal granulomas consisting of leukocytes, epithelioid cells, and Langhans' giant cells, which are frequently associated with dermal appendages, particularly dermal nerves (Figure 2). At times the granuloma may invade and actually destroy dermal nerves, a process almost pathognomonic of leprosy and that distinguishes it from other dermal granulomatous processes, particularly sarcoidosis. On acid-fast stain, few or no acid-fast bacilli (AFB) are seen in the dermis of patients with tuberculoid disease, and tuberculoid patients' peripheral blood lymphocytes regularly recognize *M leprae* in vitro. The rim of a tuberculoid macule is the preferred biopsy site for diagnostic purposes, normal-appearing skin in these patients being histologically unremarkable.

On the other end of the spectrum, patients with lepromatous leprosy have infiltrated, nodular, and plaquelike

TABLE 1.—*Features of Polar Forms of Leprosy*

Clinical Feature	*Polar Forms of Leprosy*	
	Tuberculoid	*Lepromatous*
Skin lesions	Hypopigmented, anesthetic macules with defined borders	Infiltrated nodules and plaques
Peripheral neuropathy	Early and asymmetric	Later and symmetric
Dermal histology	Granuloma with numerous lymphocytes, epithelioid cells, and foreign body giant cells: few or absent acid-fast bacilli	Highly vacuolated foamy macrophages; many acid-fast bacilli
Cell-mediated immunity to *Mycobacterium leprae*	Present	Absent
Antibodies to *M leprae*	Present about ⅔ of time	Almost invariably present
Serologic tests false-positive	No	Often

skin lesions (Figure 3). They may have loss of eyebrows and eyelashes, and their peripheral neuropathy and nerve enlargements are generally more symmetric. Skin biopsies preferably are taken from lesional areas, but normal-appearing skin will also be generally infected, the dermis showing many AFB, frequently in clusters, called globi (Figure 4), and numerous highly vacuolated fat-laden macrophages, called foam cells (Figure 5). Patients with lepromatous leprosy are anergic to *M leprae* but, unlike patients with lymphoma, carcinomatosis, or AIDS, mount normal immune responses to other antigens and have positive skin tests for purified protein derivative if concomitantly infected with *M tuberculosis* (Figure 6). Both T-cell and macrophage defects have been described in patients with lepromatous leprosy.[12-14] The *M leprae*-specific T-cell anergy in lepromatous leprosy may be either a function of an abundance of suppressor T cells or a result of "immune tolerance" from large amounts of *M leprae*-derived immunosuppressant lipids and carbohydrates.[15,16] Particular candidate molecules for this are the *M leprae*-specific phenolic glycolipid and lipoarabinomannan.[17-19]

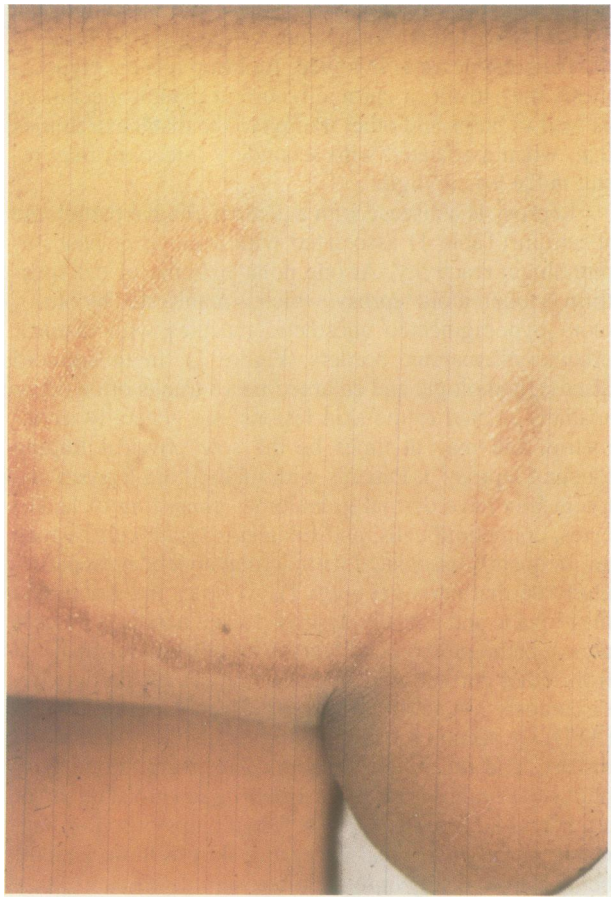

Figure 1.—A hypopigmented macule of tuberculoid leprosy shows a defined border.

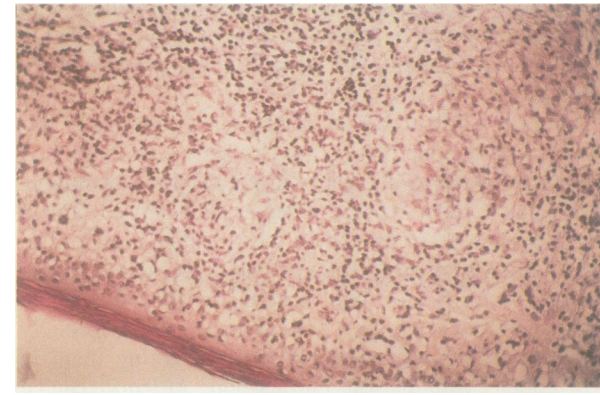

Figure 2.—The histologic appearance of the dermis in tuberculoid leprosy is shown (hematoxylin and eosin stain).

Patients in the middle of the spectrum, having features of both polar forms, are said to have borderline leprosy.

Antimicrobial Therapy

There are only four drugs commonly available to treat leprosy: dapsone, clofazimine, ethionamide, and rifampin, with only rifampin being bactericidal for *M leprae* in humans. Dapsone has the virtue of being inexpensive—$1 per year for the usual 100-mg-per-day adult daily dose—and relatively nontoxic. It causes hemolysis in all patients, which may result at times in anemia, especially in patients with glucose-6-phosphate dehydrogenase deficiency, and it may be allergenic. Clofazimine is generally administered to adults in a daily dose of 50 to 100 mg or 100 mg three times a week. Unfortunately, its use results in a red-black skin discoloration that is often uneven and frequently unacceptable to light-skinned persons. Also, taking clofazimine may result in various gastrointestinal side effects. Ethionamide, 250 to

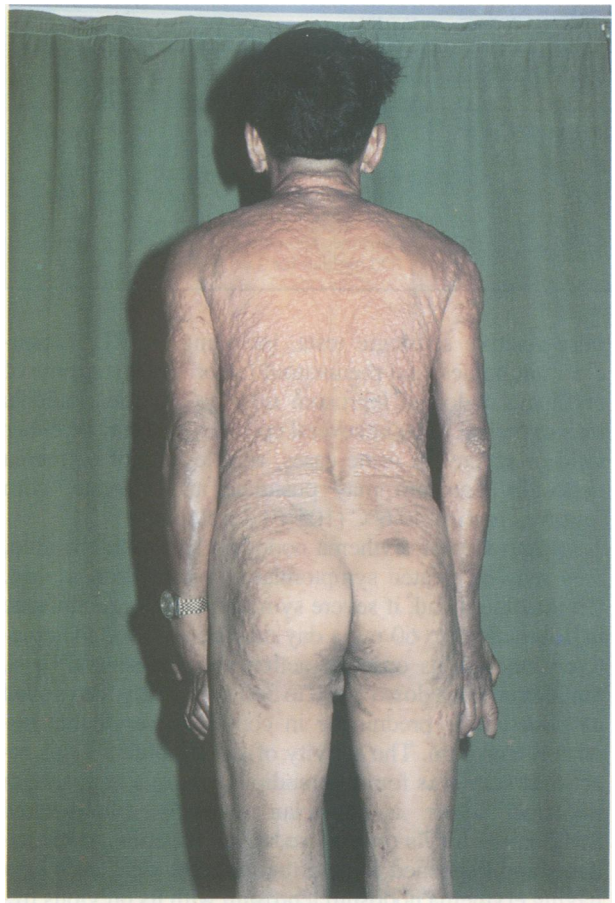

Figure 3.—The infiltrated lesions of lepromatous leprosy are shown. Note the sparing of the midline of the back, the dermis therein being 5°C warmer than at the posterior axillary line. Other warm areas—scalp, axilla, and groin—are also generally spared in lepromatous leprosy.

500 mg daily in adults, may also cause gastrointestinal irritation and, more important, liver toxicity, especially when combined with rifampin; thus, its use cannot be recommended together with rifampin in areas of the world where liver function cannot be carefully monitored. Rifampin, which also may be hepatotoxic, is unfortunately expensive: approximately $1 for a usual adult 600-mg dose. For this reason, the WHO recommends it be administered but once a month, rather than, as is done in the United States, daily.

Regimens to treat leprosy are presented in Table 2. As can be seen, my recommendations differ from those of WHO. These differences stem from judgments concerning the prevalence of dapsone resistance and the significance of bacterial persistence. The WHO regards dapsone resistance to be of sufficient concern that its efficacy alone cannot be relied on.[20] I have found no primary dapsone resistance in the United States of any clinical importance, however.[21] The WHO considers that although viable *M leprae* can be obtained from the skin of treated patients after prolonged therapy,[22,23] the risk of these drug-sensitive "persisters" relapsing is minimal; I remain unconvinced of this. On these grounds, the WHO recommends three drugs for lepromatous disease and finite periods of therapy,[20] whereas I and other clinicians use only two drugs but with lifelong treatment.

Recently minocycline hydrochloride,[24,25] some of the newer macrolide antibiotics, particularly clarithromycin,[25-27] and a number of fluoroquinolones[28,29] have been found to be bactericidal against *M leprae* in mice. Minocycline and two of the fluoroquinolones, pefloxacin and ofloxacin, have been found to be more rapidly effective than either dapsone or clofazimine in clinical trials.[30,31] Thus there are prospects that new antimicrobials may emerge to further improve the therapy for leprosy.

Slit-skin smears are a useful means of determining disease severity and the efficacy of treatment. Skin smears are obtained by scraping the dermis with a scalpel or razor blade and are examined microscopically both for the density of organisms (bacteriologic index) and the percentage of organisms that stain evenly (morphologic index).

Generally smears are taken from six different skin sites, traditionally the earlobes, anterior knees, and posterior elbows—sites that can be cleared of blood by pinching—but other lesional areas may be substituted. Patients with lepromatous leprosy generally have an initial bacteriologic index of 4+ to 6+, which falls by 1+ per year of effective therapy, becoming zero generally at about five years. The fall of the morphologic index corresponds with

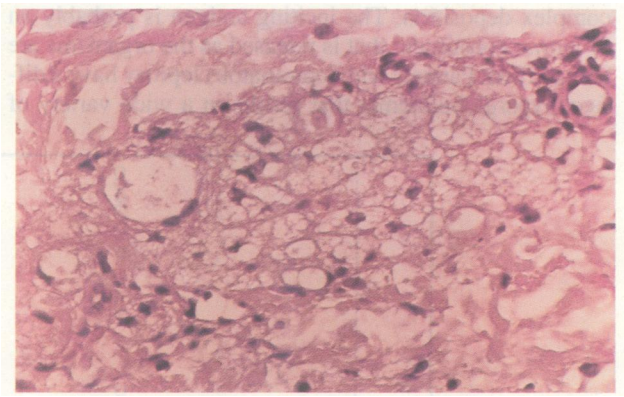

Figure 4.—An acid-fast stain of the dermis in untreated lepromatous leprosy shows the numerous clustered bacilli, or globi.

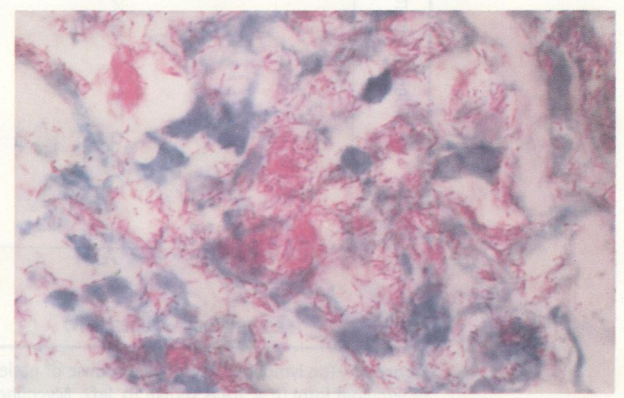

Figure 5.—The dermis in lepromatous leprosy shows foam cells (hematoxylin and eosin stain).

TABLE 2.—*Recommendations for Therapy in Adult Patients With Leprosy*

Source	Treatment of Leprosy	
	Tuberculoid	*Lepromatous*
World Health Organization	Dapsone, 100 mg/day, and rifampin, 600 mg/mo for 6 mo	Dapsone, 100 mg/day, with clofazimine, 50 mg/day, and supervised rifampin, 600 mg plus clofazimine, 300 mg/mo; therapy to be continued at least 2 yr or until smears negative (generally 5 yr)
Gelber.....	Dapsone, 100 mg/day for 5 yr	Dapsone, 100 mg/day for life, and rifampin, 600 mg/day for 3 yr

the loss of *M leprae* viability and is far more rapid, becoming zero in days or weeks with rifampin treatment and in a few months with dapsone use.

Reactional States in Leprosy and Their Treatment

During the course of lepromatous leprosy, patients may have a reaction, generally while on therapy, erythema nodosum leprosum or lepra type 2 reaction. This syndrome consists of one or a number of the following manifestations: painful papules of the skin that may ulcerate, fever, neuritis, lymphadenitis, orchitis in men, uveitis, glomerulonephritis with red cells and red cell casts in the urine, and occasionally arthritis, particularly of large joints. Erythema nodosum leprosum is histologically a vasculitis or panniculitis thought to be due to immune complex deposition. The inciting antigen is probably an *M leprae* constituent that is released as the organisms are being killed. Patients with lepromatous leprosy have a diffuse hyperglobulinemia that results in a wide variety of false-positive serologic tests, including VDRL, antinuclear antibodies, and rheumatoid factor. The syndrome of erythema nodosum leprosum may be variable. Patients may experience one or several episodes that may be either mild or severe. In some cases, skin lesions of erythema nodosum leprosum may pustulate and ulcerate, with fevers as high as 40.6°C (105°F) developing.

If episodes of erythema nodosum leprosum are mild, they may be treated symptomatically only with aspirin. On the other hand, if severe symptoms occur, prednisone in doses of 40 to 60 mg a day may be required. Alternatively, though its onset of action requires several days, thalidomide in a dose of 100 to 300 mg nightly has proved as effective as prednisone in controlling erythema nodosum leprosum. The activity of thalidomide for this reactional state was found serendipitously in a leprosarium in Israel where a physician regularly administered thalidomide for its original sedative properties to his patients and happened to note that patients were no longer having erythema nodosum leprosum with its previous fre-

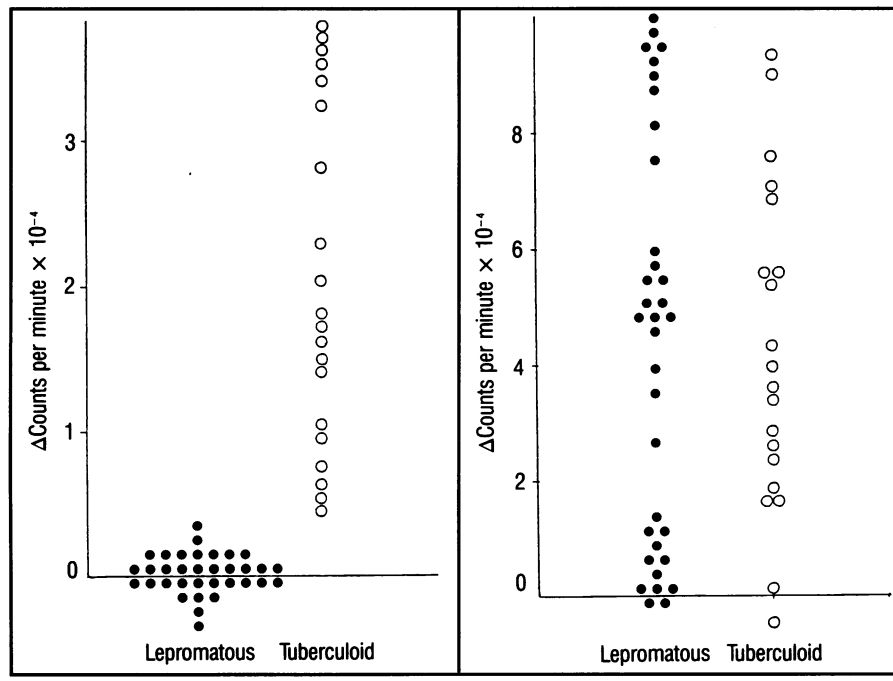

Figure 6.—The lymphoproliferative response of patients with lepromatous leprosy (n = 34) and those with the tuberculoid form (n = 20) is shown to, **left,** *Mycobacterium leprae* antigen and, **right,** purified-protein-derivative antigen, in both cases using 1 μg per culture. The findings demonstrate the *M leprae*-specific anergy of lepromatous leprosy.

quency. Before the recognition that it caused severe birth defects, particularly phocomelia, when given to pregnant women, thalidomide was considered the ideal tranquilizer, principally because the median lethal dose for thalidomide is almost infinitely large. For men and nonpregnant women, thalidomide is safe, with its only side effects other than tranquilization being mild leukopenia, constipation, and rare peripheral neuropathy affecting shoulder and particularly hip girdle strength. It has been postulated that thalidomide is active in erythema nodosum leprosum and perhaps other immunologically mediated disorders by impairing immunoglobulin M synthesis, polymorphonuclear leukocyte migration, and the production of tumor necrosis factor.[32,33] For lepromatous leprosy, thalidomide is available for the control of erythema nodosum leprosum in men and nonfertile women under an investigational license held at the G.W. Long Hansen's Disease Center with coinvestigators at a number of regional centers, including the four on the West Coast.

Patients in the middle of the spectrum either before therapy (downgrading reaction) or after the initiation of therapy (reversal reaction) may have another sort of reaction, a lepra type 1 reaction, associated with signs of inflammation in old borderline lesions, the development of new inflamed skin lesions, neuritis, and low-grade fever. These reactions can only be treated with corticosteroids—generally 40 to 60 mg per day of prednisone initially—on which therapy patients must be maintained (preferably at lower levels) for a few months after control lest recurrence occurs. For this reason, steroid therapy should be initiated only for lepra type 1 reactions in the presence of neuritis, skin inflammation that threatens to ulcerate, or if cosmetically important sites, such as the face, are involved. The initiation of steroids within 24 hours of such a reaction involving nerves is required to prevent irreversible sequelae and is one of the few medical emergencies in patients with leprosy.

Patients with a form of leprosy known as diffuse lepromatosis, which is almost exclusively found in western Mexico, in which they generally have no visible nodules but diffuse dermal thickening, may have a distinct reaction called Lucio's phenomenon. Shallow ulcerations develop on the lower extremities that, when multiple, commonly result in secondary infection, bacteremia, and death due to sepsis. It is not clear if this is a regional variant of erythema nodosum leprosum or a result of small arteriolar occlusion.[34] For this reaction, although steroids may be of some benefit, neither corticosteroids nor thalidomide have proved reliably effective. Because Lucio's phenomenon may be the result of immune complexes, particularly cryoglobulin complexes, exchange transfusion for severe cases has been recommended.[35] Because death results from bacteremia, we have found careful wound care and appropriate antimicrobials effective.

Serologic Tests in Leprosy

In 1981 Hunter and Brennan found that *M leprae* contained a specific phenolic glycolipid, its terminal trisaccharide and particularly its terminal glucose being unique among mycobacteria and, indeed, in nature.[36] In patients with leprosy, antibodies develop to this phenolic glycolipid, mainly of the immunoglobulin M class. We found that lepromatous patients almost invariably (96%) had this antibody, whereas patients with other mycobacterial diseases, whether tuberculosis or atypical mycobacterial infections, did not.[37] Unfortunately, in patients with tuberculoid leprosy, in whom we often do not find organisms and at times have difficulty distinguishing from patients with other types of granulomatous dermatitis, only about two thirds of the time are these antibodies present.

There is generally a fall in antibody titer with effective treatment, untreated lepromatous patients having a higher mean antibody titer than those who have had several years of therapy.[37] The rate of fall of titers after the initiation of effective treatment in individual patients is so variable that the usefulness of monitoring titers to assess the efficacy of therapy is limited. On the other hand, when a precipitous rise in titers occurs, this has been found to coincide with disease relapse.[37] Unfortunately, a loss of antibody to *M leprae*-specific phenolic glycolipid cannot be used as a measure of cure because patients who have been treated for many years and who no longer harbor detectable *M leprae* in the skin may still frequently have significant, though low, levels of antibody.[37]

Another area where serologic tests may prove useful is in identifying patients incubating disease before clinical manifestations. Unfortunately, in many locales there is a high prevalence of serum antibody to this phenolic glycolipid that, if used to select patients for the initiation of therapy, would result in the treatment of a considerable number of persons who might never get the disease to prevent it developing in a few. Prevalence of the antibody in a population, however, may prove the most sensitive assessment of *M leprae* transmission within a population and consequently provide the means to monitor the rise and fall of endemicity. The prevalence of antibody in a population vaccinated against leprosy may also provide the most sensitive means currently available to monitor vaccine efficacy.

Vaccine Prophylaxis

Bacille Calmette-Guérin vaccination for the two major mycobacterial diseases, tuberculosis and leprosy, has demonstrated variable efficacy. For leprosy it is moderately to minimally effective.[38-42] Because there is considerable evidence that mycobacterial lipids and sugars, particularly phenolic glycolipid and lipoarabinomannan,[17-19] inhibit both lymphocytic and macrophage function, we have postulated that protein molecules of *M leprae* devoid of these immunosuppressive molecules may prove to be superior vaccines against *M leprae* and, by analogy, also perhaps against *M tuberculosis.* Indeed, we have found that certain *M leprae* proteins including various cell wall protein preparations, soluble proteins, partially purified proteins, and bioengineered proteins, when used as vaccines in mice, afford protection against subsequent *M leprae* infection, and certain of these provide a protection that is consistently more effective and

longer lasting than killing *M leprae* itself.[43,44] These studies provide hope that in the future a newer generation of *M leprae* human vaccines based on *M leprae* proteins may prove superior to bacille Calmette-Guérin vaccine and generally efficacious.

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